M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 17, 2000

SUBJECT: Summary report of FDA analytical survey of approved NDA/ANDA inhalation solutions marketed in Low Density Polyethylene (LDPE) containers without a protective overwrap.

To: The Record

From: Michael Smela, Jr.
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Division of Chemistry 1
Office of Generic Drugs

Background: Dey Laboratories, Inc. initiated a large scale recall of inhalation solutions in the summer of 1999 due to contamination of the products with 1-phenoxy-2-propanol. The recall was conducted with the knowledge of the FDA and followed a Health Hazard Evaluation of the situation in FDA/CDER. The Office of Generic Drugs (OGD) was concerned that other inhalation solution products that have been approved over the years may be similarly situated as the Dey products. It was decided to conduct a survey of marketed products.

Sampling: The OGD and the Division of Pulmonary and Allergy Drug Products (DPADP) identified all approved applications for LDPE packaged inhalation solutions that do not have protective overwraps. A total of 23 ANDAs and 1 NDA were identified covering 5 different drug substances (Attachment 1). It was learned that all Isoetharine products as well as Metaproterenol Sulfate of ——— were currently not in distribution. The CDER Office of Compliance issued an assignment to the appropriate ORA field offices for sampling of representative lots of the remaining products which were covered by 7 ANDAs and 1 NDA. A total of 37 samples representing 38 lots of the various drug products were collected and forwarded to ORA's Pacific Regional Laboratory Northwest for analysis.

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Analysis: Samples were screened for potential volatile and semi-volatile contaminants using Gas Chromatography/Mass Spectrophotometry with a sensitivity of approximately 0.5 ppm (part per million). A similarly sensitive screening for potential contaminants was conducted using High Performance Liquid Chromatography (HPLC) with special emphasis for vanillin, 2-phenoxyethanol and 1-phenoxy-2-propanol as these compounds have previously been detected as contaminants in these types of products. Analytical responses were further characterized for chemical identification to the extent possible.

Results: Of the 37 samples tested, 29 tested positive for potential packaging chemical contamination (Attachment 2). The remaining 8 samples were free of impurities under the test conditions. One sample (Metaproterenol Sulfate ——, tested positive for 2-phenoxyethanol at 1.7 ppm. This finding is considered insignificant as this issue had been previously addressed in a CDER recommendation for a Class 3 recall which —— did not implement. The lot expired 6/00. The remaining samples were found to contain varying levels of 5 different chemical contaminants which are presumed to be packaging ingressers. Several samples are listed as —— Metaproterenol Sulfate and it is assumed that these lots are being distributed under the —— with generic labeling as —— and does not hold its own approved ANDA for this drug.

EVALUATION: The findings relative to the 5 chemical contaminants which are presumed to be packaging chemicals were submitted for Health Hazard Evaluation to DPADP (Attachment 3). Completed Health Hazard Evaluations as amended have been returned (Attachment 4).

Future Plans: It has yet to be decided what effect, if any, the Health Hazard Evaluation should have on the indicated drug products, and by what means such decisions, if any, should be communicated to the application holders. ——

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Attachment 1 Listing of Approved Applications

Application #	Drug Substance	Holder	Strength
89817	Isoetharine HCL	Dey	0.08%
89818	Isoetharine HCL	Dey	0.1%
89819	Isoetharine HCL	Dey	0.17%
89820	Isoetharine HCL	Dey	0.25%
89614	Isoetharine HCL	Astra	0.062%
89615	Isoetharine HCL	Astra	0.125%
89616	Isoetharine HCL	Astra	0.167%
89617	Isoetharine HCL	Astra	0.2%
89618	Isoetharine HCL	Astra	0.25%
87396	Isoetharine HCL	Roxane	0.1%
87025	Isoetharine HCL	Roxane	0.125%
88226	Isoetharine HCL	Roxane	0.167%
87324	Isoetharine HCL	Roxane	0.2%
88275	Isoetharine HCL	Roxane	0.25%
74209	Cromolyn Sodium	Dey	1%
74755	Ipratropium Bromide	Dey	0.02%
72652	Albuterol Sulfate	Dey	0.083%
71855	Metaproterenol Sulfate	ALPharma	0.4%
71726	Metaproterenol Sulfate	ALPharma	0.6%
18761	Metaproterenol Sulfate	Boehringer Ingelheim	0.4%, 0.6%
71275	Metaproterenol Sulfate	Astra	0.4%
71018	Metaproterenol Sulfate	Astra	0.6%
71786	Metaproterenol Sulfate	Dey	0.4%
70804	Metaproterenol Sulfate	Dey	0.6%

Attachment 2 Test Results

Sample #	Manufac.	drug	lot / exp	HPLC Results	GC/MSD Results
60605		metaproterenol		Clean* (0.5ppm LOQ)	~0.6ppm DEGBE
60606		metaproterenol		Clean (0.5ppm LOQ)	Nothing above ~0.5ppm
60607		metaproterenol		Clean (0.5ppm LOQ)	Nothing above ~0.5ppm
60608		metaproterenol		Clean (0.5ppm LOQ)	1.2ppm DEGBE ~0.6ppm Benzophenone
60609		metaproterenol		Clean (0.5ppm LOQ)	~0.5ppm DEGBE
60610		metaproterenol		Clean (0.5ppm LOQ)	~0.5ppm DEGBE
60611		metaproterenol		Clean (0.5ppm LOQ)	Nothing above ~0.5ppm
67155		metaproterenol		Clean (0.5ppm LOQ)	Nothing above ~0.5ppm
67156		metaproterenol		Clean (0.5ppm LOQ)	Nothing above ~0.5ppm
67157		metaproterenol		Clean (0.5ppm LOQ)	Nothing above ~0.5ppm
67158		metaproterenol		Clean (0.5ppm LOQ)	1.2ppm DEGBE ~0.5ppm Benzophenone
67159		metaproterenol		Clean (0.5ppm LOQ)	1.2ppm DEGBE
18524		metaproterenol		2.0ppm 2-HMPP**	~5ppm total PEG's ~2.2ppm 2-HMPP
67899		metaproterenol		1.0ppm 2-HMPP	~4ppm total PEG's ~1.0ppm 2-HMPP
67900		metaproterenol		0.33ppm 2-HMPP	~5ppm total PEG's
67902-1		metaproterenol		0.44ppm 2-HMPP	~2ppm total PEG's
67902-2		metaproterenol		0.52ppm 2-HMPP	~4ppm total PEG's
44103		metaproterenol		Clean (0.5ppm LOQ)	~0.6ppm DEGBE
44104		metaproterenol		Clean (0.5ppm LOQ)	2.1ppm DEGBE
47716		metaproterenol		Clean (0.5ppm LOQ)	~0.7ppm DEGBE
47727		metaproterenol		Clean (0.5ppm LOQ)	~0.5ppm DEGBE
47728		albuterol sulfate		Clean (0.5ppm LOQ)	0.89ppm DEGBE 1.6ppm DEGEEA
47729		albuterol sulfate		Clean (0.5ppm LOQ)	Nothing above ~0.5ppm
47730		ipratropium bromide		Clean (0.5ppm LOQ)	1.2ppm DEGBE
47731		ipratropium bromide		Clean (0.5ppm LOQ)	Nothing above ~0.5ppm
47732		cromolyn sodium		Clean (0.5ppm LOQ)	1.5ppm DEGBE
47733		cromolyn sodium		Clean (0.5ppm LOQ)	~0.6ppm DEGBE
67901		metaproterenol		Clean (0.5ppm LOQ)	1.3ppm DEGBE
69771		metaproterenol		Clean (0.5ppm LOQ)	1.2ppm DEGBE
69772		metaproterenol		Clean (0.5ppm LOQ)	2.9ppm DEGBE
69773		metaproterenol		1.7 ppm 2-PE	1.6 ppm 2-PE
69774		metaproterenol		Clean (0.5ppm LOQ)	1.5ppm DEGBE
69775		albuterol sulfate		Clean (0.5ppm LOQ)	1.3ppm DEGBE
69776		albuterol sulfate		Clean (0.5ppm LOQ)	1.1ppm DEGBE
69777		ipratropium bromide		Clean (0.5ppm LOQ)	1.5ppm DEGBE 0.36ppm DEGEEA
69778		ipratropium bromide		Clean (0.5ppm LOQ)	~0.5ppm DEGBE and DEGEEA
69779		cromolyn sodium		Clean (0.5ppm LOQ)	3.8ppm DEGBE
69780		cromolyn sodium		Clean (0.5ppm LOQ)	2.6ppm DEGBE

*Clean = No 2-phenoxyethanol, 1-phenoxyisopropanol or vanillin above the 0.5ppm limit of quant

**2-HMPP = 2-Hydroxy-2-methylpropiophenone - id'd by GC/MS and quantified by HPLC

PEG's = Polyethylene glycols HO-(CH2-CH2-O)n-H where n is ~4-8 (no standards available)

DEGBE = Di(ethylene glycol) butyl ether = 2-(2-butoxyethoxy) ethanol

DEGEEA = Di(ethylene glycol) ethyl ether acetate = 2-(2-ethoxyethoxy) ethanol acetate

Attachment 3 Request for Health Hazard Evaluation

1. **Benzophenone**...Found in 2 lots of ——— at 0.5-0.6ppm.

2. **Low Molecular Weight Polyethylene Glycols (n=4-8)**

Found in 3 lots of ——— 0.4% Metaproterenol at 4-5ppm and 2 lots of ——— 0.6% Metaproterenol at 2-4ppm.

3. **DEGBE (Di(ethylene glycol) butyl ether, or 2-(2-butoxyethoxy)ethanol):**

Found in 1 lot of 0.6% ——— Metaproterenol at 0.6ppm
Found in 3 lots of 0.6% ——Metaproterenol at 1.2 ppm.
Found in 2 lots of 0.4% —— Metaproterenol at 0.5ppm
Found in 4 lots of 0.4% ——Metaproterenol at 0.5-1.5ppm
Found in 4 lots of 0.6% —— Metaproterenol at 1.5-2.9ppm
Found in 3 lots of 0.083% —— Albuterol at 0.9-1.3ppm
Found in 3 lots of 0.02% —— Ipratropium at 0.5-1.5ppm
Found in 4 lots of 1% ——Cromolyn at 0.6-3.8ppm

4. **DEGEEA (Di(ethylene glycol) ethyl ether acetate, or 2-(2-ethoxyethoxy) ethanol acetate):**

Found in 1 lot of ——Albuterol at 1.6ppm
Found in 2 lots of — Ipratropium at 0.5-0.9ppm

5. **2-HMPP (2-Hydroxy-2-methylpropiophenone):**

Found in 3 lots of 0.4% ——— Metaproterenol at 0.3-2ppm
Found in 2 lots of 0.6% ——— Metaproterenol at 0.4-0.5ppm

Note: 2-HMPP is not specifically listed as a process impurity for the synthesis of the drug substance. However, it is an old file and the reviewer believes that is is possible that this impurity may be formed as a by-product of the synthesis.

Attachment 4 Health Hazard Evaluations

MEDICAL OFFICER CONSULTATION

Date: August 4, 2000

To: OGD/Regulatory Support Branch HFD-615

From: Eugene J. Sullivan, MD, FCCP
Medical Officer, Division of Pulmonary and Allergy Drug Products

Luqi Pei, PhD, DVM
Pharmacologist/Toxicologist, DPADP

Through: Robin Huff, PhD
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Through: Badrul Chowdhury, MD, PhD
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Through: Robert Meyer, MD
Director, DPADP

Subject: Health Hazard Evaluation for non-overwrapped, LDPE-packaged inhalation solutions

General Information

NDA/IND#: Multiple.
Sponsor: Multiple.
Protocol: N/A.
Drug Product: Albuterol sulfate, Cromolyn sodium, Ipratropium bromide, Metaproterenol sulfate.
Request From: Office of Generic Drugs.
Materials: Cover letter and 2-page summary of the analytical survey.

Background

At the request of OGD, an analytical survey of non-overwrapped, LDPE-packaged inhalation solutions was performed by ORA's Pacific Regional Laboratory. The purpose of the survey was to detect potential chemical contamination of these products. Samples of various drug products (see consult request) were obtained and assayed using Gas Chromatography/Mass Spectrometry and High Performance Liquid Chromatography with special emphasis on three chemicals which have been previously detected in these types of products: vanillin, 2-phenoxyethanol, and 1-phenoxy-2-propanol.

Of the 37 samples, 29 tested positive for chemical contamination. One sample tested positive for 2-phenoxyethanol at 1.7ppm. This finding has already been addressed by CDER in its recommendation

for a Class 3 recall of a [redacted] product. The remaining samples were found to contain varying levels of 5 different chemical contaminants: benzophenone, low molecular weight polyethylene glycols, DEGBE [Di(ethylene glycol) butyl ether or 2-(2-butoxyethoxy)ethanol)], DEGEEA [(Di(ethylene glycol) ethyl ether acetate or 2-(2-ethoxyethoxy) ethanol acetate], and 2-HMPP [2-hydroxy-2-methylpropiophenone]. These five contaminants were different than the three chemicals that the analytic method was specifically designed to detect. OGD has requested that DPADP perform a Health Hazard Evaluation.

In order to address this evaluation, DPADP convened a multidisciplinary group including representatives from the CMC, pharm/tox and medical disciplines.

Specific Comments

Four of the five chemicals identified are assumed to represent contaminants that have leached into the drug product from outside the LDPE vial. Labeling and packaging materials may be the source of some or all of these four contaminants. The fifth, 2-HMPP is presumed to be a synthetic impurity. The amount of information available regarding the toxicologic profiles of these five compounds is variable. Although the toxicologic evaluations of these chemicals are incomplete, there is no specific evidence to suggest that they pose a significant toxicologic risk at the concentrations detected. There is no information available regarding the potential for these chemicals to act as spasmogens in the airways of normal subjects or patients with asthma or chronic obstructive pulmonary disease. However, the concentrations of the contaminants detected were low (≤ 5ppm).

A completed Health Hazard Evaluation form is attached to this memorandum. The presence of these contaminants is concerning.

[redacted] The available toxicology data for each contaminant is summarized below, along with our opinion regarding the potential for human toxicity for each contaminant.

1. Benzophenone

Benzophenone is a respiratory irritant, and this irritancy is a dose-dependent phenomenon. The expected low level of exposure for benzophenone (0.12 µg/kg/day) is far below its permissible workplace level of 710 µg/kg/day recommended by the American Industrial Hygiene Association. This suggests that benzophenone at the observed levels would be unlikely to irritate the respiratory tract and trigger bronchospasms in COPD and asthmatic patients.

2. Polyethylene glycols

The safety of polyethylene glycols (PEGs), including PEG 200 and PEG 400, as inactive ingredients in drug products, has been established. Formulations of the approved and marketed products using PEGs include parental, oral, topical, dental, nasal and other preparations. PEGs are not components of any approved inhalation drug products, but reasonably sufficient data show that the low levels of PEGs (≤ 5 ppm) does not cause significant safety concern. Laboratory studies have shown that small molecular PEGs such as PEG 600 have no effect on the respiratory tract at an inhalation dose of 1.4 mg/kg/day in dogs. (This level is 1,400 times greater than the expected dose of 1 µg/kg/day in humans.) Clinical trials with formulations containing PEG 600 did not show any evidence of bronchospasm associated with the treatment. Because PEGs of small molecular weights are expected to possess similar toxicity profiles, available information suggests that the observed levels of PEGs are unlikely to be irritating to the respiratory system and thus, unlikely to cause bronchospasm in the intended populations.

3. DEGBE [Di(ethylene glycol)butyl ether]

DEGBE is the most prevalent leachable found in the survey. A total of 24 lots of drug products were found to contain the compound. DEGBE is apparently a respiratory irritant at high concentrations, but laboratory studies show that DEGBE has no effect on the respiratory tract at an air concentration of 18 ppm (26 mg/kg/day) for 5 weeks in rats. These inhalation toxicity studies show that the liver is the target organ of DEGBE toxicity. The inhalation NOAEL value is 3 mg/kg/day. This value is 5,000 times the expected exposure levels in humans (0.6 µg/kg/day). [Note: this NOAEL is based upon a 5-week study. It is possible that the NOAEL could decrease with chronic exposure.] These data show that DEGBE is not likely to irritate the respiratory tract and trigger bronchospasm in the intended population.

4. DEGEEA [Di(ethylene glycol)ethyl Ether Acetate

DEGEEA was found in a total of three lots of the inhalation solutions. Available information for DEGEEA is too limited to conduct a sound safety evaluation of the compound. The following information was found in databases:

DEGEEA is a solvent and a plasticizer. It irritates the eyes, mucous membranes and upper respiratory tract at high concentrations. Rats and guinea pigs exposed to an essentially saturated atmosphere at room temperature for 8 hours (approximately 207 mg/kg) revealed injury to the lung and kidneys at gross autopsy, but detailed information about the injuries is not available. No occupational exposure standards or permissible

levels for DEGEEA are available. The Hazardous Substance Data Bank (HSDB) states that "no hygienic standard of permissible exposure... has been suggested, nor would one seem necessary in view of the low volatility and the nature of the material".

The above information is insufficient to establish the safety of DEGEEA in asthmatic and COPD patients. The HSDB statement is inapplicable to the drug products of interest because DEGEEA will be delivered to the lung through the administration of these drug products. Although the expected exposure in the patient is relatively low (0.32 µg/kg/day), the possibility of DEGEEA triggering bronchospasm in asthmatic and COPD patients cannot be excluded due to the irritability of the compound. Because of the lack of data on the dose-response relationship for the irritability of DEGEEA, caution should be applied to the safety assessment of the compound.

5. 2-HMPP (2-hydroxy-2-methylpropiophenone)

Five lots of inhalation solutions were found to contain 0.3 - 2.0 ppm of 2-HMPP, a synthesis impurity. The safety evaluation of 2-HMPP should follow the ICH guidelines on the qualification of impurities. The 2-HMPP levels (0.05%) in the products of interest is below the identification and qualification threshold of 0.1%. This renders the 2-HMPP levels acceptable and no further discussion is necessary.

Conclusion:

A preclinical health hazard evaluation indicates that the levels of benzophenone, PEGs, DEGBE, and 2-HMPP do not raise sufficient safety concerns in the intended population to warrant a recall of the products involving these contaminants.

The absence of any known occurrence of harm to a patient and the absence of specific data to demonstrate toxic potential of these chemicals at the concentrations detected preclude a more aggressive recall action. However, several issues raise particular concern. First, the potential for these chemicals to cause bronchospasm, particularly in the patient populations using these drug products, is unknown. Second, it is not clear whether the products were tested at the end of their shelf-life. It is possible that the concentration of contaminants might be greater at the end of the expiry. Third, this analysis has demonstrated that chemical contaminants can and do leach into these drug products. It is possible that additional chemicals were also present, but were not detected by the assays used. Further,

- future changes in the materials used in labeling and packaging may result in contamination with different chemicals.

We believe that these issues are concerning enough to merit aggressive measures to ensure that future LDPE-packaged inhalation solutions remain free of leachable chemicals. It is quite possible that chemical contamination of inhalation solutions may have clinical consequences. The current absence of data to establish such clinical consequences is not completely reassuring. Because the potential adverse effect of these chemicals (bronchospasm) is also the indication for which the drug products are used, it would be very difficult to establish any link between the chemicals and bronchospasm. In light of the concerns regarding these and other chemical contaminants as well as the data that suggests that asthma mortality rates are increasing, it is advisable to make all efforts to assure the purity of these drug products. We recommend that you initiate efforts, separate and in addition to the proposed development of a guidance document on this permeability issue, to ensure that all single dose inhalation drug products in LDPE vials have a secondary full overwrap and not have paper labeling directly applied to them.